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EXAMINER

ROMEO, DAVID S

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 11/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/063,617

Applicant(s)

EATON ET AL.

Examiner

David S Romeo

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 0902.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed 09/10/2002 has been entered. Claims 1-13 are pending and being examined.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC §§ 101, 112

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

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The present claims are drawn to or encompass an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 110 (PRO1753) or comprising an amino acid sequence having a recited % identity thereto.

The present specification discloses a nucleotide sequence (SEQ ID NO: 109) of a native sequence PRO1753 cDNA, wherein SEQ ID NO: 109 is a clone designated as "DNA68883-1691" (paragraph 0135). FIG. 110 shows the amino acid sequence (SEQ ID NO: 110) derived from the coding sequence of SEQ ID NO: 109 shown in FIG. 109 (paragraph 0136). The specification discloses uses for PRO polynucleotides and polypeptides in general (paragraphs 0316-0360; pages 86-100). Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution) discloses that DNA68883-1691 is more highly expressed in esophageal tumor as compared to normal esophagus (page 143).

The present specification discloses that secreted proteins and membrane-bound proteins and receptors have widely varying activities (paragraphs 0002-0004). This finding establishes that secreted proteins and membrane-bound proteins and receptors have very diverse functions and makes it clear that classification of a protein as a secreted protein or a membrane-bound protein or receptor does not identify it as having a specific function. The specification provides no basis for concluding which, if any, of the varied activities of secreted proteins and membrane-bound proteins and receptors is possessed by the PRO1753 polypeptide. There is no evidence that a skilled artisan would have appreciated the identification of the PRO1753 polypeptide, without more, would have suggested any specific patentable utility.

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The disclosed uses for PRO polynucleotides and polypeptides in general (paragraphs 0316-0360) are not specific to the PRO1753 polypeptide.

Although the specification discloses that DNA68883-1691 is more highly expressed in esophageal tumor as compared to normal esophagus (page 143), the
5 specification provides no information regarding the absolute values of the differences in transcript levels and provides no information regarding level of expression, activity, or role of the PRO1753 polypeptide in cancer. The art demonstrates that increased transcript levels do not necessarily correlate with increased polypeptide levels. See Haynes (U), who studied more than 80 proteins relatively homogeneous in half-life and
10 expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (page 1863, second paragraph, and Figure 1).

15 Hancock (V) states that "the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling" (full paragraph 2).

Therefore, the art indicates that transcript levels are not always correlated with protein levels.

20 Furthermore, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu (W) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a

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microarray (p. 408, middle of right column). Hu discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

In addition, Wang (X) indicates that differential display is the first of many steps required in the discovery of a novel pharmacological target, especially given that the function of the factor is most likely unknown. Therefore, further action should be taken to characterize the functions of a particular gene of interest, including ... validation for the importance of the gene in disease processes. See page 279, column 2, full paragraph 1.

Finally, one skilled in the art recognizes that although structural similarity can serve to classify a protein as related to other known proteins this classification is insufficient to establish a function or biological significance for the protein because ancient duplications and rearrangements of protein-coding segments have resulted in complex gene family relationships. Duplications can be tandem or dispersed and can involve entire coding regions or modules that correspond to folded protein domains. As a result, gene products may acquire new specificities, altered recognition properties, or modified functions. Extreme proliferation of some families within an organism, perhaps at the expense of other families, may correspond to functional innovations during evolution. See Henikoff (Y), page 609, Abstract. Accordingly, one skilled in the art would not accept mere homology as establishing a function of protein because gene products may acquire new specificities, altered recognition properties, or modified

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functions. Rather, homology complements experimental data accumulated for the homologous protein in understanding the homologous protein's biological role.

Although, the presence of a protein module in a protein of interest adds potential insight into its function and guides experiments, insight into the biological function of a protein

5 cannot be automated. However, homology can be used to guide further research. See Henikoff (Y), paragraph bridging pages 613-614, through page 614, paragraph bridging columns 1-2.

Haynes, Hancock, Hu, Wang, and Henikoff are evidence that the specification fails to disclose enough information about the invention to make its usefulness

10 immediately apparent to those familiar with the technological field of the invention. This countervailing evidence shows that the skilled artisan would have a legitimate basis to doubt the utility of the PRO1753 polypeptide. The skilled artisan would not know if PRO1753 polypeptide expression could, should, or would be upregulated, down-regulated, or unchanged in cancer. Therefore, the disclosure that DNA68883-1691 is
15 more highly expressed in esophageal tumor as compared to normal esophagus does not impute a specific, substantial, and credible utility to the PRO1753 polypeptide. Based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a
20 "real world" context of use are not substantial utilities. Therefore, the increased transcript levels of DNA68883-1691 in esophageal tumor as compared to normal esophagus does not establish a substantial or real-world use for the claimed polypeptide. Thus, the present disclosure is simply a starting point for further research and investigation into

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potential practical uses of the claimed polypeptides. See Brenner v. Manson, 148

U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

5 "The basic quid pro quo contemplated by the Constitution and the
Congress for granting a patent monopoly is the benefit derived by
the public from an invention with substantial utility", "[u]nless and
until a process is refined and developed to this point-where specific
benefit exists in currently available form-there is insufficient
justification for permitting an applicant to engross what may prove
10 to be a broad field", and "a patent is not a hunting license", "[i]t is
not a reward for the search, but compensation for its successful
conclusion."

Claims 1-13 are also rejected under 35 U.S.C. 112, first paragraph. Specifically,
since the claimed invention is not supported by either a specific and substantial asserted
15 utility or a well established utility for the reasons set forth above, one skilled in the art
clearly would not know how to use the claimed invention.

Claims 1-5, 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to
comply with the enablement requirement. The claim(s) contains subject matter which
20 was not described in the specification in such a way as to enable one skilled in the art to
which it pertains, or with which it is most nearly connected, to make and/or use the
invention.

The claims are directed to or encompass a polypeptide having at least 80% amino
acid sequence identity to the polypeptide of SEQ ID NO: 110, to said polypeptide lacking
25 its associated signal peptide, or to the extracellular domain thereof. The claims are broad
because they do not require the claimed polypeptide to be identical to the disclosed
PRO1753 polypeptide and because the claims have no functional limitation.

The first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The PRO1753 polypeptide appears to be a secreted polypeptide. However, the present specification discloses that secreted proteins and membrane-bound proteins and receptors have widely varying activities (paragraphs 0002-0004). This finding establishes that secreted proteins and membrane-bound proteins and receptors have very diverse functions and makes it clear that classification of a protein as a secreted protein or a membrane-bound protein or receptor does not identify it as having a specific function. The specification provides no basis for concluding which, if any, of the varied activities of secreted proteins and membrane-bound proteins and receptors is possessed by the PRO1753 polypeptide. There is no evidence that a skilled artisan would have appreciated the identification of the PRO1753 polypeptide, without more, would have suggested any specific use. Therefore, the knowledge that a protein is a secreted polypeptide does not provide predictability about its function.

There are no working examples of polypeptides with an amino acid sequence less than 100% identical to the amino acid sequence of SEQ ID NO: 110. The examiner is

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aware that working examples are not required. Lack of a working example, however, is a factor to be considered, especially in cases involving an unpredictable and undeveloped art.

The specification does not provide guidance for using polypeptides related to (i.e.,
5 80%-99% identity) but not identical to SEQ ID NO: 110. Specifically, the instant specification does not identify those amino acid residues in the amino acid sequence of PRO1753 which are essential for its biological activity and structural integrity and those residues which are either expendable or substitutable. In the absence of this information, the skilled artisan is left to an unduly extensive amount of random, trial and error
10 experimentation wherein a polypeptide comprising the amino acid sequence of SEQ ID NO: 110 is randomly mutated and randomly assayed for a useful activity. Further, there does not appear to be a functionally and structurally analogous protein which has been identified in the prior art for which this information is known and could be extrapolated to the PRO1753 polypeptide by analogy. In any case, while a specification need not
15 disclose what is well known in the art, that rule does not excuse an applicant from providing a complete disclosure. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. Based on the teachings of the present specification, the skilled artisan would not know how to use such non-identical polypeptides absent undue
20 experimentation. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the amino acid

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sequence of SEQ ID NO: 110 which are required for the functional and structural integrity of the PRO1753 polypeptide. It is this additional characterization of that single disclosed, naturally occurring protein that constitutes undue experimentation.

For these reasons, which include the complexity and unpredictability of the nature
5 of the invention and art in terms of the diversity of secreted proteins and membrane-bound proteins and receptors and lack of knowledge about function(s) associated with the PRO1753 polypeptide and its variants, the lack of working examples, the lack of direction or guidance for using polypeptides that are not identical to SEQ ID NO: 110, and the breadth of the claims for structure without function, it would require undue
10 experimentation to use the invention commensurate in scope with the claims.

Claims 1-5, 12, 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one
15 skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to or encompass a polypeptide having at least 80%, 85%, 90%, 95% or 99% sequence identity with a SEQ ID NO: 110, to said SEQ ID NO: lacking its associated signal peptide, or to the extracellular domain of said SEQ ID NO:.
20 The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

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To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

5 Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 110, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

10 Claims 1-6, 9, 10, 12, 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15 The PRO1753 polypeptide is disclosed as a soluble or secreted protein, and is not disclosed as being expressed on a cell surface. Accordingly, the limitation "extracellular domain" is indefinite, as the art does not recognize soluble or secreted proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain ... lacking its associated signal sequence" is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal
20 sequences are cleaved from said domains in the process of secretion from the cell. The metes and bounds are not clearly set forth.

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Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571)272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHT FAX NUMBERS:

BEFORE FINAL (703) 872-9306

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CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.



DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
NOVEMBER 9, 2004